

Based on the foregoing, Applicant(s) submit that the rejection of claims 1, 12, and 21 under 35 U.S.C. § 112, second paragraph should be withdrawn.

35 U.S.C. 102 (b) -- Garman, Rohatgi, and Wei

Claims 1, 3-4, 6-8, 10, 12-13, and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Garman et al. (GB 2278356) (hereinafter "Garman") with support from Rohatgi et al. (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) (hereinafter "Rohatgi") and Wei et al. (Anal. Chem (5/1994), vol. 66 (9), pages 1500-1506) (hereinafter "Wei").

The Examiner essentially states that:

Garman teaches a protease substrate (p. 13) and assay method using the substrate wherein the substrate is cleaved by an enzyme and an increase in fluorescence is observed (pp. 14-15), wherein the substrate comprises a flexible peptide and two fluorescence groups which are fluorescein and tetramethylrhodamine (substrate D on pages 13-14). Rohatgi provides support that both fluorescein and tetramethylrhodamine are capable of dye-stacking (p. 1696 and 1699) and Wei provides support that fluorescein and tetramethylrhodamine attached to a peptide can interact to "essentially" self-quench the fluorescence groups (p. 1503, Figure 3A), therefore claims 1, 3, 6-8, 12, 15-18 are anticipated. Garman's substrate comprises Peptide II (p. 13), which is 14 amino acids in length. Garman teaches that each amino acid is 3.8 Å, therefore a peptide of 14 amino acids is about 53.2 Å, therefore if the C-terminus and N-terminus are labeled with the dye groups (i.e., the furthest distance possible), the dye groups will be separated by at most 53.2 Å, therefore claims 4 and 13 are anticipated. Wei also provides support that distances of 47-54 Å allow up to 70% quenching of fluorescence (pp. 1503-1504). Staphylococcal V8 protease is an aspartic protease, therefore claims 10 is anticipated.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 (citing *Verdegaal Bros. V. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

Garman does not disclose dimerization, but discloses only energy transfer. Accordingly, the reference does not describe every element of the claimed invention. Applicants submit that it is improper to cite Rohatgi and Wei as support for Garman because an anticipation rejection must be supported by a single reference. See MPEP 706.02 (a).

Based on the foregoing, Applicant(s) submit that the cited reference cannot support a 35 U.S.C. 102(b) rejection and respectfully requests that the rejection be withdrawn.

### 35 U.S.C. §103 Obviousness Rejections

According to MPEP 2142, to establish a case of *prima facie* obviousness, three basic criteria must be met: 1) there must be some suggestion or motivation, either in the references or generally known to one of skill in the art, to modify or combine the reference teachings, 2) there must be reasonable expectation of success, and 3) the prior art references must teach or suggest all the claim limitations. The ability to modify the method of the references is not sufficient. The reference(s) must provide a motivation or reason for making the changes. *Ex parte Chicago Rawhide Manufacturing Co.*, 226 USPQ 438 (PTO Bd. App. 1984).

### 35 U.S.C. 103(a) – Garman, Rohatgi, Wei, and Komoriya

Claims 1-8 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garman et al. (GB 2278356) (hereinafter “Garman”) as supported by Rohatgi et al. (J. Phys. Chem (6/1966) vol. 70 (6), pages 1695-1701) (hereinafter “Rohatgi”) and Wei et al. (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506) (hereinafter “Wei”), and in view of Komoriya et al. (US 5,714,342) (hereinafter “Komoriya”).

The Examiner states in part:

It would have been obvious to one of ordinary skill in the art at the time of invention to have labeled the substrate (Peptide II) of Garman, as supported by Rohatgi and Wei with the rhodamine combination taught by Komoriya to result in the “at least” 10-fold increase in fluorescence where the motivation would have been to use a combination of dyes known to result in high fluorescence intensity in order to optimize, or increase sensitivity, of the method. It would also have been obvious to one of ordinary skill in the art at the time of invention to have doubly labeled the substrate of Garman, as supported by Rohatgi and Wei with any of the fluorophores taught by Komoriya to be satisfactory for homo-double-labeling of a protease substrate (e.g. any of those shown in Table 9 except fluorescein) where the motivation would have been to facilitate use of the substrate in methods of detection, as suggested by Komoriya’s teaching that homo-double-labeled substrates supply an advantage in methods of detecting enzymes, as set forth above.

Applicants respectfully submit that the references cannot support a case of *prima facie* obviousness as to the claims because, among other possible reasons, the cited references do not provide a motivation or suggestion to provide a substrate having dimerizing pairs of fluorescent moieties in Garman because the stated purpose of Garman is to provide an improved method of

preparing a fluorescence resonance energy transfer substrate. *See, e.g.*, Garman at p. 2, 3<sup>rd</sup> full paragraph. As is described in the present specification at p. 4, line 17 to p. 5, line 10, energy transfer is a different type of quenching from dimerization. Accordingly, there is no motivation to combine the dimerizing moieties of Rohatgi, Wei, and Komoriya with the substrates of Garman.

For these reasons, Applicants submit that the cited references will not support a 103(a) rejection of the claimed invention and request that the rejection be withdrawn.

35 U.S.C. 103(a) – Garman, Rohatgi, Wei, and Heath

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garman et al. (GB 2278356) (hereinafter “Garman”) as supported by Rohatgi et al. (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) (hereinafter “Rohatgi”) and Wei et al. (Anal. Chem (5/1994), vol. 66 (9), pages 1500-1506) (hereinafter “Wei”), in view of Komoriya et al. (US 5,714,342) (hereinafter “Komoriya”), as applied to claims 1-8 and 10-18 above, and further in view of Heath, Jr., et al. (US 5,235,039) (hereinafter “Heath, Jr.”).

The Examiner states in part:

It would have been obvious to one of ordinary skill in the art at the time of invention to have substituted the octapeptide of Heath for Peptide II in the substrate and method of Garman, Rohatgi, Wei, and Komoriya where the motivation would have been to measure vertebrate collagenase, as taught by Heath (col. 10, lines 35-51).

Applicants respectfully submit that the references cannot support a case of *prima facie* obviousness as to the claims because, among other possible reasons, the cited references do not provide a motivation or suggestion to provide a substrate having dimerizing pairs of fluorescent moieties in Garman because the stated purpose of Garman is to provide an improved method of preparing a fluorescence resonance energy transfer substrate. *See, e.g.*, Garman at p. 2, 3<sup>rd</sup> full paragraph. As is described in the present specification at p. 4, line 17 to p. 5, line 10, energy transfer is a different type of quenching from dimerization. Accordingly, there is no motivation to combine the dimerizing moieties of Rohatgi, Wei, and Komoriya with the energy transfer substrates of Garman, but limited to the octapeptide substrate of Heath.

For these reasons, Applicants submit that the cited references will not support a 103(a) rejection of the claimed invention and request that the rejection be withdrawn.

35 U.S.C. 103(a) – Garman, Rohatgi, Wei, and Manafi

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Garman et al. (GB 2278356) (hereinafter “Garman”) as supported by Rohatgi et al. (J. Phys. Chem (6/1966) vol. 70 (6), pages 1695-1701) (hereinafter “Rohatgi”) and Wei et al. (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506) (hereinafter “Wei”), and in view of Manafi et al. (Microbiol. Reviews (9/1991), vol. 55 (3), pages 335-348) (hereinafter “Manafi”).

The Examiner states in part:

It would have been obvious to one of ordinary skill in the art at the time of invention to have detected Staphylococcus using the substrate and method of Garman where the motivation would have been to use cleavage of a specific fluorescent substrate to detect and differentiate Staphylococcus, as suggested by Manafi’s teaching that specific Staphylococcus species can be detected with a fluorescent substrate.

Applicants respectfully submit that the references cannot support a case of *prima facie* obviousness as to the claims because, among other possible reasons, the cited references do not provide a motivation or suggestion to provide a substrate having dimerizing pairs of fluorescent moieties in Garman because the stated purpose of Garman is to provide an improved method of preparing a fluorescence resonance energy transfer substrate. *See, e.g.*, Garman at p. 2, 3<sup>rd</sup> full paragraph. As is described in the present specification at p. 4, line 17 to p. 5, line 10, energy transfer is a different type of quenching from dimerization. Accordingly, there is no motivation to combine the dimerizing moieties of Rohatgi and Wei with the energy transfer substrates of Garman, and the non-dimerizing fluorescent microbial detection systems of Manafi.

For these reasons, Applicants submit that the cited references will not support a 103(a) rejection of the claimed invention and request that the rejection be withdrawn.

In addition to the foregoing arguments, Applicants submit that a dependent claim should be considered allowable when its parent claim is allowed. *In re McCain*, 101 USPQ 411 (CCPA 1954). Accordingly, provided independent claims 1, 12 and 21 are allowed, all claims depending therefrom should also be allowed.

The Examiner is invited to contact Applicants’ attorney if the Examiner believes any remaining questions or issues could be resolved.

Based on the foregoing, it is submitted that the application is in condition for allowance. Withdrawal of the rejections under 35 USC 102, 103 and 112 is requested.

Examination and reconsideration of the claims are requested. Allowance of the claims at an early date is solicited.

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Respectfully submitted,

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- b) cleaving one or more of said cleavable bonds of the peptide by said characteristic enzyme to release the fluorescence dye groups from dye dimerization or stacking, thereby producing an increase in fluorescence intensity which indicates the presence of said microorganism.

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